Vol. 97 (2002) (SUPPLEMENT A), S1–S2

respiratoryMEDICINE

Introduction
The symposium that never occurred: pre-clinical and clinical development of sibenadet

S. I. RENNARD

University of Nebraska Medical Center, U.S.A.

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Its prevalence has risen greatly over the last several decades and will continue to rise, becoming the third largest cause of death and the fifth largest cause of morbidity by the year 2020. It is a relentlessly progressive disorder. While current treatments for COPD offer some benefits to patients, they do not (with the exception of smoking cessation) affect the rate at which lung function is lost and they only partially address patient symptoms.

The following articles describe the results of the development programme for a novel dual D_2 dopamine receptor, β_2-adrenoceptor agonist, sibenadet (Viozan™), which was specifically developed to address the unmet needs of the symptomatic patient with COPD. Although the development of sibenadet has been discontinued due to disappointing efficacy findings, this compendium is remarkable in a number of respects.

First, the articles summarize 'symposia that never occurred', substituting for both a planned global expert roundtable meeting that did not occur due to the shocking events of 11 September 2001 in New York, and the congress symposia that would have taken place had sibenadet development been continued. AstraZeneca has, however, committed the resources to support the current supplement. This decision was taken not only because of the company commitment to publishing study findings, but also due to the recognition that lessons learned during the sibenadet development programme are important for the future development of medications to help the patient with COPD.

Second, the clinical community concerned with COPD was energized and enthusiastically awaiting sibenadet. It held promise to be the first medication with demonstrated efficacy to improve symptoms of breathlessness, cough and sputum. This triad of cardinal symptoms is a major problem for many patients that remains unaddressed by any medication. The potential to shift the paradigm of COPD treatment and assessment approaches was therefore apparent. Sibenadet was designed to improve breathlessness, cough and sputum by means of conventional beta-agonist activity, plus inhibition of airway sensory nerve activity through activation of dopaminergic receptors. As such, sibenadet was aimed at treating an unaddressed dimension in COPD.

Assessing the efficacy of sibenadet required approaches not previously used in assessing currently available bronchodilators. This necessitated the development of a tool to assess the benefit of sibenadet on the core COPD symptoms of breathlessness, cough and sputum and a novel instrument, the Breathlessness, Cough and Sputum Scale (BCSS©), was developed specifically for this purpose. The sibenadet development programme, therefore, promised a new medication for the patient with COPD, assessed using this new instrument in addition to more conventional measures.

Although sibenadet's promise in pre-clinical and early clinical trials went unfulfilled, the development programme leaves at least two key legacies, i.e. knowledge that it is possible to modify COPD symptoms with therapeutic intervention and that resultant changes can be monitored effectively using the BCSS. In this way the BCSS can be used to assess a previously poorly evaluated feature of COPD and enable evaluation of future therapies.

A third benefit of this supplement is that the reader will be able to track the development story for this novel approach from its conceptualization through pre-clinical validation, early tests in man and finally to the definitive clinical trials. These efforts represent a major investment, not only of company resources, but also of the creative energies and scientific insights of the investigators involved. The reader will be able to observe the evidence available when key decisions were made and will be able to understand something about how such

Correspondence should be addressed to: Stephen I. Rennard MD, University of Nebraska Medical Center, Department of Internal Medicine, Pulmonary and Critical Care, 9853000 Nebraska Medical Center, Omaha, NE 68198-5300, U.S.A. Tel: +1 402 559 4878 or 7313, Fax: +1 402 559 8210 or 9093.

decisions were made in the face of uncertainty. The sibenadet story, therefore, will be of interest to anyone concerned with the rational development of novel therapies. Thus, while the clinical trials did not demonstrate sufficient efficacy for the company to take sibenadet forward, the articles presented here are likely to be of considerable value to the interested reader.

Finally, many drugs that fail in development for one reason or another do not result in compiled publications such as this. AstraZeneca is to be commended for recognizing the value of the lessons learned from the sibenadet development programme and for helping to make them readily accessible through the development of this supplement.